CLAIMS:

1. A screening method for identifying a methoxyphosphonate nucleotide analogue prodrug conferring enhanced activity in a target tissue comprising:

(a) providing at least one of said prodrugs;

(b) selecting at least one therapeutic target tissue and at least one non-target tissue;

(c) administering the prodrug to the target tissue and to said at least one non-target tissue; and

(d) determining the relative activity conferred by the prodrug in the tissues in step (c).

2. The method of claim 1 wherein the activity is antiviral activity or antitumor activity.

3. The method of claim 2 wherein the activity is antiviral activity.

4. The method of claim 3 wherein the activity is anti-HIV or anti-HBV activity.

5. The method of claim 1 wherein the prodrug is a prodrug of PMPA or PMEA.

6. The method of claim 5 wherein the prodrug is a phosphonoamidate, phosphonoester or mixed phosphonoamidate/phosphonoester.

7. The method of claim 6 wherein the amidate is an amino acid amidate.

8. The method of claim 6 wherein the ester is an aryl ester.

9. The method of claim 1 further comprising selecting a prodrug having a relative activity in the target tissue that is greater than 10 times that of the non-target tissue.

10. The method of claim 1 wherein the target and non-target tissue are in an animal, the prodrug is administered to the animal and the relative activity is determined by analysis of the animal tissues after administration of the prodrug.

11. The method of claim 1 wherein activity in the target and non-target tissues is determined by assaying the amount of at least one metabolite of the prodrug in the tissues.

12. The method of claim 12 wherein the metabolite is the parental drug.

13. The method of claim 12 wherein the metabolite is the diphosphate of the parental drug.

14. The method of claim 1 wherein the target tissue is virally infected tissue and the non-target tissue is the same tissue which is not virally infected.

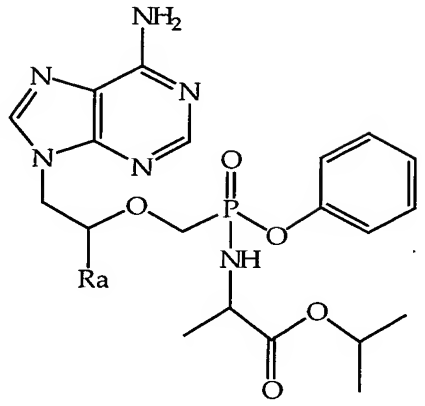
15. The method of claim 1 wherein the target tissue is lymphoid tissue and the activity is anti-HIV activity.

16. The method of claim 1 wherein the target tissue is liver and the activity is anti-HBV activity.

17. The method of claim 1 wherein the target tissue is hematological and the activity is antitumor activity.

18. The method of claim 1 wherein the target tissue is malignant and the non-target tissue is the same tissue but non-malignant.

19. A compound having the structure (1)

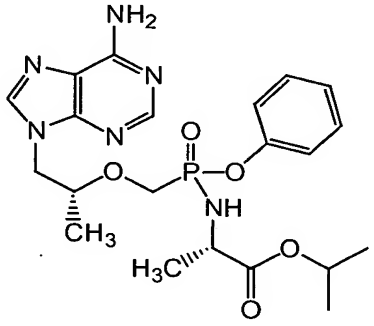


(1)

where Ra is H or methyl,

and chirally enriched compositions thereof, salts, their free base and solvates thereof.

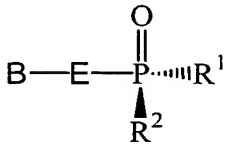
20. A compound having the structure (2)



(2)

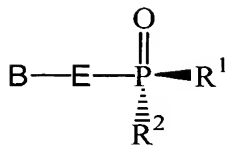
and its enriched diasteromers, salts, free base and solvates.

21. A diastereomerically enriched compound having the structure (3)



(3)

which is substantially free of the diastereomer (4)



(4)

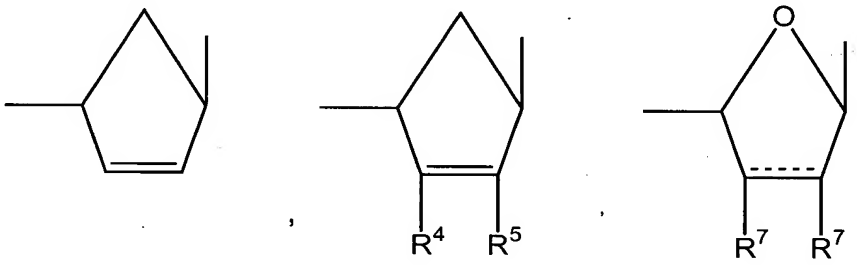
wherein

R^1 is an oxyester which is hydrolyzable *in vivo*, or hydroxyl;

B is a heterocyclic base;

R^2 is hydroxyl, or the residue of an amino acid bonded to the P atom through an amino group of the amino acid and having each carboxy substituent of the amino acid optionally esterified, but not both of R^1 and R^2 are hydroxyl;

E is $-(CH_2)_2-$, $-CH(CH_3)CH_2-$, $-CH(CH_2F)CH_2-$, $-CH(CH_2OH)CH_2-$, $-CH(CH=CH_2)CH_2-$, $-CH(C\equiv CH)CH_2-$, $-CH(CH_2N_3)CH_2-$,



$-CH(R^6)OCH(R^{6'})-$, $-CH(R^9)CH_2O-$ or $-CH(R^8)O-$, wherein the right hand bond is linked to the heterocyclic base;

the broken line represents an optional double bond;

R^4 and R^5 are independently hydrogen, hydroxy, halo, amino or a substituent having 1-5 carbon atoms selected from acyloxy, alkyoxy, alkylthio, alkylamino and dialkylamino;

R^6 and $R^{6'}$ are independently H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, or C_2-C_7 alkanoyl;

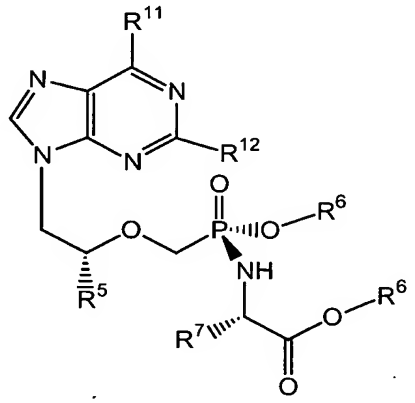
R^7 is independently H, C_1-C_6 alkyl, or are taken together to form -O- or $-CH_2-$;

R^8 is H, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl or C_1-C_6 haloalkyl; and

R^9 is H, hydroxymethyl or acyloxymethyl;

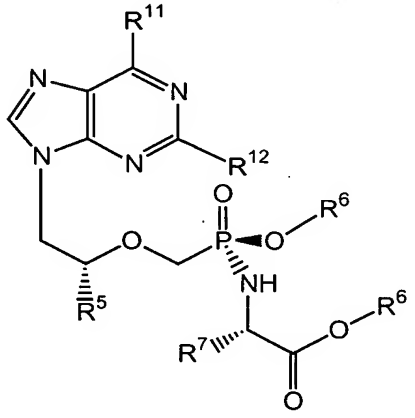
and their salts, free base, and solvates.

22. A diastereomerically enriched compound having the structure (5a)



(5a)

which is substantially free of diastereomer (5b)



(5b)

wherein

R^5 is methyl or hydrogen;

R^6 independently is H, alkyl, alkenyl, alkynyl, aryl or arylalkyl, or R^6 independently is alkyl, alkenyl, alkynyl, aryl or arylalkyl which is substituted with from 1 to 3 substituents selected from alkylamino, alkylaminoalkyl, dialkylaminoalkyl, dialkylamino, hydroxyl, oxo, halo, amino, alkylthio, alkoxy,

alkoxyalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylalkoxyalkyl, haloalkyl, nitro, nitroalkyl, azido, azidoalkyl, alkylacyl, alkylacylalkyl, carboxyl, or alkylacylamino;

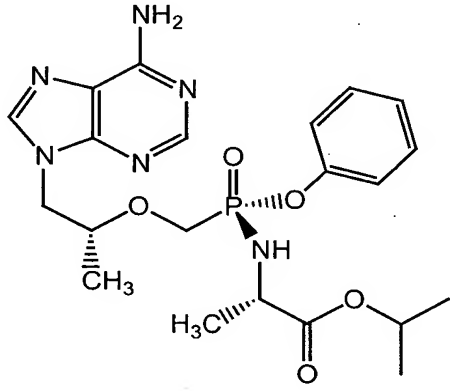
R^7 is the side chain of any naturally-occurring or pharmaceutically acceptable amino acid and which, if the side chain comprises carboxyl, the carboxyl group is optionally esterified with an alkyl or aryl group;

R^{11} is amino, alkylamino, oxo, or dialkylamino; and

R^{12} is amino or H;

and it salts, tautomers, free base and solvates.

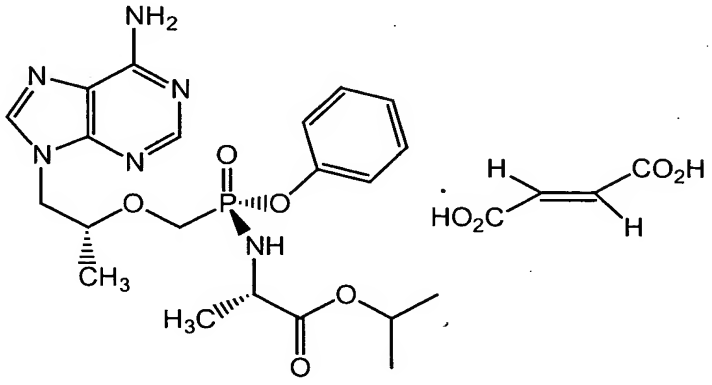
23. A compound of structure (6)



(6)

and its salts and solvates.

24. A compound of structure (7)



(7)

25. A composition comprising a compound of any of claims 19-24 and a pharmaceutically effective excipient.

26. The composition of claim 25 wherein the excipient is a gel.

27. The composition of claim 25 which is suitable for topical administration.

28. A method for antiviral therapy or prophylaxis comprising administering a compound of any of claims 19-24 in a therapeutically or prophylactically effective amount to a subject in need of such therapy or prophylaxis.

29. A method for use of magnesium alkoxide comprising reacting 9-(2-hydroxypropyl)adenine (HPA) or 9-(2-hydroxyethyl)adenine (HEA), magnesium alkoxide, and protected *p*-toluenesulfonyloxymethylphosphonate.

30. The method of claim 29 further comprising recovering PMPA or PMEA, respectively.

31. The method of claim 29 wherein the phosphonate of the *p*-toluenesulfonyloxymethylphosphonate is protected by ethyl ester.

32. The method of claim 29 wherein the alkoxide is a C_1-C_6 alkoxide.

33. The method of claim 32 wherein the alkoxide is t-butyl or isopropyl oxide.